

Abstract

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmacology & Toxicology

Student: Adéla Janoušková

Supervisor: RNDr. Jakub Hofman, Ph.D.

Title of diploma thesis: **Study on impact of selected protein kinase inhibitors on drug resistance mediated by cytochromes P450**

Pharmacokinetic drug resistance often leads to failure of an anticancer therapy. One of the mechanisms is increased efflux of drugs from tumour cells, whereas some studies suggest that increased drug conversion to an inactive metabolite might be another contributing mechanism. The aim of this work was to define the possible role of CYP3A4 and CYP2C8 enzymes in the phenomenon of pharmacokinetic resistance and to investigate the possibility of its modulation by new targeted drugs. In the first part, we used the MTT proliferation method together with HepG2 cells stably transduced with particular human enzymes and demonstrated significant involvement of CYP3A4 in docetaxel resistance. In the following part, we examined the inhibitory effects of four selected tyrosine kinase inhibitors on the CYP3A4 activity in intact cells using a commercial kit. Cobimetinib and dabrafenib showed significant inhibitory activity, while osimertinib and brivanib did not. In the final part, we demonstrated the ability of the first two mentioned drugs to modulate resistance to docetaxel mediated by CYP3A4 using the MTT assay. Our results might be used as a valuable basis for understanding the role of biotransformation enzymes in the drug resistance phenomenon. The results of the combination experiments point to the synergistic effect of the studied compounds, which could possibly be used in antitumour therapy.